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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/922,240	08/27/97	SCHREIBER S	APV-007.01

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EXAMINER	
HAUDA,K	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 08/03/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 08/922,240	Applicant(s) Schreiber et al.
	Examiner Karen M. Hauda	Group Art Unit 1632

☒ Responsive to communication(s) filed on *May 10, 1999* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-43* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment filed May 10, 1999, paper # 6 has been entered. Claims 1-43 are pending.

Specification

The objection to the specification with respect to a missing example 2 is withdrawn in view of applicant's amendment filed May 10, 1999, paper # 6.

Claim Rejections - 35 USC § 112

Claims 1-43, as originally filed, newly amended or newly added, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with the scope of the claimed invention.

Applicants argue that it was well known in the art at the time of the invention that NF-AT regulates the transcription of various cytokines that are involved in cell proliferation and that this is the mechanism for which immunosuppressants function. Applicants additionally argue that it was known that NF-AT dependent genes, such as IL-2, were known in the art to be involved in cell proliferation. Thus, applicant's conclude that one of skill in the art would readily have anticipated that inhibition of NF-AT mediated transcription in a cell would result in inhibition of

cell proliferation. Applicant's arguments have been carefully considered, but are not deemed persuasive.

Applicant's conclusion is based on a presumption that NF-AT transcription is the only gene involved in cellular proliferation. Such is not the case. Numerous growth factors have been shown in the art to stimulate cells to proliferate, such that a sterile environment for *in vitro* inhibition of calcineurin/NF-AT mediated transcription using a combination of mutated cyclophilin or FK506 binding protein and mutated cyclosporin A or FK506 respectively does not support inhibition of proliferation of all hematopoietic cells *in vivo* which are exposed to numerous different growth factors. Furthermore, the specification fails to give guidance to the skilled artisan on how to determine structural alterations which would result in mutated MBP's which inhibit proliferation of any and all hematopoietic cells upon contact with a macrolide except for that taught in Example 2 and 3. It is noted that the interaction of the mutated MBP and macrolide analog is critical to the practice of the claimed invention. Applicants argue that FK506 inhibits the production of IL-2 and, thus, inhibits T-cell proliferation. However, applicants claims are not limited to the administration of a mutated FK506 binding protein or to the inhibition of only T-cells such that this argument overcomes the rejection of record pertaining to inhibition of proliferation of hematopoietic cells using any mutated macrolide binding protein (MBP).

Applicants argue that determination of MBP expression levels is within the skill of the artisan and that the Examiner has not set forth reasoning for the criticality of the expression level parameters. To the contrary, however, the examiner has set forth the unpredictability of

determining the *in vivo* parameters for expression levels based on the importance of the interaction of the mutated MBP with a macrolide analog which bind the mutated MBP, but not the naturally occurring MBP, the breadth of the claims to any mutated MBP, the absence of working examples for *in vivo* inhibition of hematopoietic cells, the absence of working examples for any inhibition of graft vs host disease (GVHD), the state of the art with respect to inhibiting growth of hematopoietic cells and the prevention of GVHD, and the nature of the invention. Given the absence of teach of parameters for any *in vivo* treatment, and the breadth of applicants claims to any mutated MBP and administration of any MBP analog, the rejection is proper without more evidence provided by applicants.

Applicants argue that the issue with respect to *in vivo* transduction are overcome by applicant's amendments. However, it is noted that claims 2-15 still encompass *in vivo* methodology and the rejection is maintained.

Therefore, for the reasons stated above, the specification is enabled only for a method of inhibiting calcineurin/NF-AT mediated transcription *in vitro* using a combination of mutated cyclophilin or FK506 binding protein and mutated cyclosporin A or FK506 respectively.

Claims 31 and 40-43, as newly amended or newly filed, stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 remains indefinite in that the method steps of inhibiting proliferation of a sub-population of hematopoietic cells does not relate back to the preamble for treating GVHD. The method is omitting essential elements.

Claims 40-43 are indefinite because it is unclear what is encompassed within the phrase "a coding sequence consisting essentially of a coding sequence for the mutated MBP". The metes and bounds of the claim can not be determined.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda

KAREN HAUDA
PATENT EXAMINER